AL/OE-TR-1994-0150

ARMSTRONG LABORATORY

IMPROVEMENTS IN MODELING OF PULMONARY UPTAKE OF TOXICANTS

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November 1994

FINAL REPORT FOR THE PERIOD AUGUST 1994

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TECHNICAL REVIEW AND APPROVAL

AL/OE-TR-1994-0150

The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

Terry A. Childress

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave Blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	November 1994	Final -August 1994

4. TITLE AND SUBTITLE
Improvements in Modeling of Pulmonary Uptake of Toxicants

5. FUNDING NUMBERS
Contract F33615-90-C-0532
PE 62202F
PR 6302
TA 630200
WU 63020002

6. AUTHOR(S)
R. Collins

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Biodynamics International
5170 Bishop Street
Halifax, Canada B3J 1C9

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Armstrong Laboratory, Occupational and Environmental Health Directorate
Toxicology Division, Human Systems Center
Air Force Materiel Command
Wright-Patterson AFB OH 45433-7400

10. SPONSORING;MONITORING AGENCY REPORT NUMBER
AL/OE-TR-1994-0150

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

The primary objective of this technical report is to provide a rational foundation for quantitatively evaluating the importance of unsteady versus steady or quasi-steady events during uptake of chemical toxicants via the human respiratory tract. A secondary objective is to review critically the current approaches in physiologically-based pharmacokinetic (PBPK) modeling of the lung with a view to generalizing the model descriptions to encompass a broader range of exposure and physiological conditions. The secondary objective is addressed first, with a succinct review of the transport mechanisms that con operate within the respiratory tract when exposed to a concentration of chemical toxicants in the form of vapors, aerosols, and particulate matter. Functional relationships are reviewed within the context of a voluminous body of international literature bearing on this and related subjects of importance. Computational models are proposed to provide an essential complementary research tool with not only simulative but also predictive capabilities. Drawing upon this considerable background of established knowledge, one can proceed more readily with a detailed study of the very important question posed as the primary objective; namely, the establishment of an order-of-magnitude analysis resulting in a general classification scheme that identifies three major flow regimes, distinguished on the basis of whether the flow is dominated by unsteadiness, viscous effects, or the effects of convective acceleration. The report concludes with some important recommendations regarding the extrapolation of test results performed on small laboratory animals to the human context.

14. SUBJECT TERMS		15. NUMBER OF PAGES
Pulmonary Ventilation	Transport Mechanisms	29
Unsteady Flows	Mathematical Modeling	16. PRICE CODE
Toxicology of Animals and Humans		

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UL

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

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PREFACE

The research reported in this document was conducted by Richard Collins, Ph.D., Biodynamics International, under a subcontract to ManTech Environmental Technology, Inc., in support of the Toxic Hazards Research Unit (THRU). The THRU is the contractor-operated effort of the Toxicology Division, Occupational and Environmental Health Directorate, Armstrong Laboratory, located at Wright-Patterson Air Force Base, Ohio, and is operated under Department of the Air Force Contract No. F33615-90-0532. Allen Vinegar, Ph.D., Manager of the THRU's Biological Simulation Section, coordinated this effort. Lt Col Terry A. Childress served as the Contract Technical Monitor.

The research described herein was conducted in August 1994, and describes factors relevant to modeling the uptake of chemical toxicants by the lung during brief exposures where unsteady state events prevail.

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IMPROVEMENTS IN MODELING OF PULMONARY UPTAKE OF TOXICANTS

Richard Collins

ABSTRACT

The primary objective of this technical report is to provide a rational foundation for quantitatively evaluating the importance of unsteady versus steady or quasi-steady events during uptake of chemical toxicants via the human respiratory tract.

A secondary objective is to review critically the current approaches in physiologically based pharmacokinetic (PBPK) modeling of the lung with a view to generalizing the model descriptions to encompass a broader range of exposure and physiological conditions.

In the following sections, the secondary objective is addressed first, with a succinct review of the transport mechanisms that can operate within the respiratory tract when exposed to a concentration of chemical toxicants in the form of vapors, aerosols, and particulate matter. Functional relationships are reviewed within the context of a voluminous body of international literature bearing on this and related subjects of importance.

Computational models are proposed to provide an essential complementary research tool with not only simulative but also predictive capabilities.

Drawing upon this considerable background of established knowledge, one can proceed more readily with a detailed study of the very important question posed as the primary objective; namely, the establishment of an order-of-magnitude analysis resulting in a general classification scheme that identifies three major flow regimes, distinguished on the basis of whether the flow is dominated by unsteadiness, viscous effects, or the effects of convective acceleration.

The report concludes with some important recommendations regarding the extrapolation of test results performed on small laboratory animals to the human context.

1. INTRODUCTION

Physiologically-based pharmacokinetic (PBPK) modeling of the pulmonary uptake of vapors, aerosols, and particulates draws on several interrelated scientific disciplines. These include biofluid dynamics, tissue mechanics, biochemistry, biophysics, physiology, and mathematics, culminating in the mathematical formulation and computational solutions of the equations of mass continuity, momentum, and energy as

embodied in nonlinear simultaneous systems of partial differential equations with associated initial and boundary conditions.

Multidisciplinary teamwork is essential for such detailed investigations, both experimental and theoretical, into the underlying mechanisms governing such complex human biological systems. In practice, as much experimentation as possible is performed upon animals as a surrogate for humans. Prior to initiating each new experimental program, it is useful and highly advisable to formulate a series of models of progressively increasing mathematical complexity. This serves a dual function by providing: (a) a basis for the rational design of an experimental progr · · in which all the governing biophysical and physiological parameters and variables may be evaluated to prescribed levels of accuracy, and (b) a framework into which these data may be incorporated and interpreted. Quantitative comparisons of model predictions with observed laboratory measurements serve to corroborate the realistic foundation of successful models, permitting the latter to be usefully employed to predict responses to new situations in lieu of conducting further costly laboratory testing.

In the event that the quantitative comparisons between model and experiment are not satisfactory, the two may require revision through an interactive process until the predictions of the model reflect the reality of the observed phenomena under investigation. This process is universal to all branches of scientific research and has recently been summarized in the context of PBPK modeling in a chapter by Leung (1993).

The first step in the formulation of a realistic model is the development of a working hypothesis for the presumed mechanisms of, in the present case, uptake of toxicants by the lungs in the forms of: (a) vapors, (b) aerosols, and (c) particulate matter. At the same time, based on logical principles of biophysics and physiology, one may identify the primary and eventually the secondary and tertiary parameters and variables that need to be taken into account in such a model. The process may be accomplished in successive phases of increasing complexity, gaining valuable experience upon the completion of each phase of the overall program. Alternatively, one may enter the project at a more advanced phase at the outset by building upon and by improving the elements of known successful models by either refining the assumptions made in those earlier models and/or by generalizing or adapting them to the new situations of interest.

With this general framework in mind, we will summarize in the following sections the general nature of PBPK models of the lung previously developed for purposes of predicting pulmonary uptake under (quasi-) steady state conditions. We will then propose refinements of the single flow-limited compartmental model to encompass more general and more realistic geometries, possible interactions with other organ systems, and possible generalizations to deal with acute, short-term exposures to toxicants of the three forms cited above.

2 PRESENT METHODS OF MODELING THE LUNG

In currently used PBPK models, the uptake function of the lung is idealized in the form of a single flow-limited compartment with a unidirectional alveolar ventilation. Uptake of vapors depends on the alveolar ventilation, cardiac output, and partitioning of the uptake chemical between blood and air. The model currently utilized was developed using the general structure of Ramsey and Anderson (1984) in order to provide quantitative descriptions of the uptake, distribution, metabolism and elimination of xenobiotic substances.

Typically, the mass balance of chemical A_L in the lung at any instant in time is described by a differential equation (Vinegar et al. 1990 b) of the form:

$$\frac{d}{dt} A_L = \underset{\text{(air via lungs)}}{Q_{ALV}(C_{INH} - C_{EXH})} + \underset{\text{(blood via lungs)}}{Q_{BL}(C_V - C_A)}$$

$$+ \underset{\text{(air across lung tissue)}}{PA(C_{PL} - C_L/P_{LA})} - \underset{\text{(loss due to metabolism)}}{V_{MAXL} \cdot C_A / (K_M + C_A)}$$

In addition, Vinegar et al. (1990 a) report measurements of minute alveolar ventilation rates QPT which were then correlated for an anatomical dead space V_D by a term

$$V_D(t) = 0.3 \quad QPT(t)_{\text{min for all time}}$$

to yield an effective value QP of alveolar ventilation in the form

$$QP(t) = QPT(t) - V_D$$

Cardiac output was then assumed proportional to the effective alveolar ventilation QP in the form

$$QC(t) = K_C \cdot QP(t)$$

It can be readily corroborated from the above that the lung appears to have been modeled in its simplest form, that of a single rigid-walled compartment with a dead space volume proportional to 30% of the minimum alveolar ventilation rate. It has been aptly pointed out by Gearheart et al. (1993) that indirect estimation of (metabolic) parameters from "fits" to a PBPK gas uptake model will depend for their success on the adequacy of the model structure. A true test of the structural adequacy, and indeed the usefulness of the model will be its general capability of predicting responses accurately over a sufficiently wide range of parameter values, surpassing that of the laboratory experiments themselves.

The question which is now posed is to ascertain the applicability of this single compartmental model to a class of more generalized pulmonary flows for which uptake of toxicants may not yet have reached a "steady state."

Such cases would relate to sudden and acute pulmonary exposure to a toxicant over a short duration, or, alternatively, to abrupt cessation of and subsequent recovery from such exposure. In either case, the pulmonary respiration and circulation undergo a substantial transition phase, the details of which are needed to assess quantitatively the associated risks.

In the following section, we will return to first principles, examining in some detail the expected response of the lung to highly dynamic changes in a number of key variables, as a means of suggesting that it may be of use in such situations to envisage a modified model structure which more fully accounts for the physiological interactions which will come into play in this more complex transitory phase.

Initially, the proposed improvements in the PBPK model will be related to the uptake of vapors, and extended only later to the more complicated uptake of liquid aerosols and solid particulate matter.

3. GENERAL OVERVIEW OF DYNAMIC PULMONARY VENTILATION AND VAPOR UPTAKE

Conventionally, the lung is divided into an alveolar compartment of uniform gas concentration wherein gas exchange with the blood takes place by diffusion, and a dead space V_D in which no gas exchange occurs.

However, ventilation in the physiological range involves mass transport by both convection and diffusion. It is widely accepted that (bulk flow) convection dominates in the larger diameter airways where flow velocities are larger; while diffusion is more significant at the level of the terminal bronchioles and alveoli, where vapor transit times are longer. There, mass transport develops primarily due to concentration gradients.

Pulmonary airflow profiles in the largest airways are flatter than the parabolic profiles characteristic of fully developed laminar Poiseuille flow. Such flows are likely to become turbulent as they pass through successive bifurcations along the tracheobronchial tree, engendering chaotic eddy currents which enhance mixing before developing a more laminar character as the flow progresses further downstream. This process, which is well known in classical fluid mechanics, has been described in its pulmonary context by Hamilton (1986).

The beating of the heart further contributes to airway (cardiogenic) mixing as the mechanical oscillations of the heart produce vibration of the walls of the airways (West et al. 1961). The degree of mixing which results may be taken as largely independent of heart rate (Dreschler et al. 1984). Indeed, such cardiac oscillations can theoretically enhance gas mixing in the airway of the dog by 1000% (Slutsky 1981) through the coupled effects of molecular diffusion and augmented convective transport.

In the smaller airways, where the flow is laminar, Taylor dispersion promotes enhanced radial diffusive mixing in adjacent annular rings as a result of local concentration gradients, in addition to axial mixing along the length of the airway. This tends to produce a bi-directional flow: the components with the higher alveolar concentration are transported outward along the walls of the airway, while the components with the higher mouth concentration appear to move toward the alveoli along the center core of the airway.

The process is cyclic and highly dynamic. Following an inspiration, the "tongue" of the O_2 pulse from the mouth extends down the airway, diffusing out to the wall, while at the same time, CO_2 diffuses in toward the center of the airway. The latter CO_2-rich air is then carried out toward the mouth during expiration, while O_2 diffuses into the tongue of the pulse as CO_2 diffuses outward. The process is repeated at each new cycle, and is cumulative so that total mixing is augmented, particularly at higher frequencies, even for small tidal volumes less than the dead space.

It has been proposed by Lehr (1980) that the different regions of the lung do not inflate uniformly, but may at any time be up to 180° out of phase with one another. Indeed, stroboscopic photography of excised dog lungs indicates a "Pendelluft" movement with significantly different time constants (resistance × compliance) for different individual airway units, engendering retrograde flows. Very similar predictions came out of the computations of Collins et al. (1979) for blood flow in the lung as a direct consequence of significant measured differences in the anatomical structures and wall compliances of the pulmonary vasculature. They successfully mathematically modeled the flow profiles within the five pulmonary interconnected lobes of the pulmonary circulation.

The asymmetry of the airway architecture and material properties can induce gas exchange in regions whose anatomical dead space V_D is less than the global dead space. In such regions with tidal volumes $V_T < V_D$, adequate alveolar ventilation could obtain without resorting to diffusive transport.

Steady-state exchange is proportional to tidal volume V_T minus dead space volume V_D and no steady state gas exchange occurs for $V_T \leq V_D$. According to Mitzner (1986), this conclusion is based on the assumption that gases traverse the dead space with a blunt flow profile (velocity constant over the airway cross-section) during the breathing cycle. Under such conditions, a small tidal volume V_T could not traverse a large dead space volume V_D. However, the velocity profile is not blunt or flat, but rather tongue-shaped, as discussed earlier. Thus, in this context, some appreciable alveolar ventilations and gas exchange can occur for $V_T < V_D$, a result which could not be modeled readily using a simple one- or two-compartment idealization of a steady-state pulmonary airflow.

In fact, it would appear that this bi-directional axial dispersion, or spreading of the gas front into a tongue along the tube (airway) axis during both inspiration and expiration, contributes significantly to the gas mixing process. A corresponding model then should include branching networks of idealized airway tube segments, with varying airway path lengths and corresponding transit times. Schroter and Sudlow (1969) have measured significantly different flow velocity profiles during inspiration and expiration in a physical branched airway model.

Accordingly, an improved global model is proposed for vapor uptake reflecting this inherent asymmetry over the the two halves of the breathing cycle, as flow streamlines cannot be precisely retraced between inspiration and expiration. The true anatomical dimensions, branching characteristics and physical properties of the distensible airways may be used to characterize the underlying mechanisms responsible for the overall axial dispersion of the flow profiles. From these, realistic gas mixing rates can be computed for a variety of unsteady pulmonary flow regimes.

4. DIFFUSION AND SETTLING OF AEROSOL PARTICLES IN THE PULMONARY AIRWAYS

According to Hext et al. (1993), inhalation represents one of the major routes by which humans can be exposed to foreign materials. These may then be readily absorbed or may react directly with adjacent tissues within the body. The successful experimentalist requires a quantitative understanding of the anatomy of the respiratory tract, the mechanisms of deposition of liquid (aerosol) or solid (particulate) matter and the species differences between the experimental animal and humans.

It is quite common for irritant toxic aerosols and particulate matter to influence considerably the breathing patterns of test animals, possibly reducing the respiratory rate by 80% This reduction can be concentration-related and response relationships can be plotted, for example, as a function of reflex response and/or bronchoconstriction. For liquid aerosols, solubility in humidified saturated atmospheres must be accounted for.

4.1 Transport Mechanisms

Deposition of particles within the respiratory tract is governed by five principal mechanisms: inertial impaction, gravitational sedimentation, Brownian diffusion and interception and electrostatic precipitation. The particle size and density relative to air are important in assessing the relative roles of these mechanisms in various regions of the respiratory tract.

Experimental results indicate that, for a single-breath delivery, the fraction of inhaled aerosol recovered closely follows an exponential function of breath-holding time for particle diameters ranging from 0.1μ to 0.8μ. Multi-exponential recovery curves are required for larger particles (Goldberg et al. 1981). Axial dispersion effects were incorporated by Yu et al. (1979) into their model for the analysis of loss of aerosol at different depths within the respiratory tract during inhalation and exhalation.

Larger particles of density different than air will not follow the flow streamlines of the inhaled pulmonary airflow. They will tend to deposit in the upper respiratory bronchi, where they can be moved mouthward into the esophagus by *mucociliary transport.*

4.2 Mucociliary Clearance

It has been observed that peak expiratory flow rates are systematically greater than corresponding peak inspiratory rates (Chang 1986). These different flow rates produce biased air-mucus shear forces favoring mouthward movement of mucus or sputum. But an important role may also be played by vagal stimulation of ciliary beating via efferent receptors. Such clearance mechanisms appear to operate during coughing. Enhancement of tracheal mucus clearance rate (TMCR) is most pronounced for breathing frequencies in the range of 11 - 15 Hz in anesthetized dogs, reaching peak values of 340% of control at 13 Hz (King et al. 1984). The velocity of mucus movement is proportional to

$$\delta V_T f^{1.5} (R - 1)$$

where δ is the thickness of the mucus layer, V_T is the tidal volume, f is frequency, and R is the ratio of peak expiratory to peak inspiratory flow rate (Chang et al. 1987).

5. FORMULATION OF A PROPOSED COMPUTATIONAL MODEL FOR HUMAN PULMONARY DYNAMICS

A complete branching model of the respiratory system is proposed on the basis of detailed anatomical measurements (Fredberg et al. 1978). A quasi one-dimensional formulation for the coupled fluid/wall interaction can be resolved numerically using a modified two-step Lax-Wendroff finite-difference technique. This model can subsequently be used to estimate the regional deposition of fine aerosol particles in the human lung.

Preliminary theoretical models of particle deposition coupled with experimental studies appear to corroborate the overall importance of particle size (Hext et al. 1993). Particle-laden air, inhaled through the nose, finds its way through to the ends of the trachea, where the branching of the airways begins; extending eventually down through the bronchi and bronchioles to the alveolar ducts and sacs. In the Landahl (1950) model of the respiratory tract, eleven primary regions have been identified, along with their average anatomical dimensions and corresponding air velocities. It will remain to associate with these the corresponding mechanical properties of wall elasticity or compliance for use in the mathematical model to be formulated.

As the particles entrained in the airflow do not have the same density as the surrounding air, their trajectories will not follow the aerodynamic streamlines. Particularly at bifurcations and flow dividers, where the curved streamlines predispose to the development of secondary flows, the centrifugal forces on such particles will push them laterally out toward the walls where they may deposit by impact and be captured.

As the airways continue their branching with successive generations, the cross-sectional area of the respiratory network increases dramatically. Air velocities decrease from 150 cm/sec at the trachea to about 2 cm/sec at the terminal bronchioles. It is especially in this region of slowly moving flow that one would expect an increased influence on particle deposition due to the action of sedimentation and Brownian diffusion.

To a lesser extent, electrical charges associated with particles dispersed into the air by grinding or combustion may cause particle aggregation and a concomitant alteration in the effective particle size distribution, with their consequences on particle deposition patterns.

Thermal forces are likely even less important. Although the temperature in the respiratory tract may rise slightly during inhalation, these minimal temperature differences are thought to have only a minor effect upon particle deposition due to Brownian motion (Morrow 1960).

5.1 Mathematical formulation

The first task is to determine the flow patterns of air in the respiratory network. The fluid equations of mass continuity and momentum must be solved in conjunction with a realistic "law of the wall" which relates local cross-section of the airways to instantaneous transmural pressures as a function of local wall properties (modulus of elasticity). Special provisions can be made for airway collapse under sporadic conditions of negative transmural pressure.

The governing equations are solved numerically in a manner similar to that used by Collins et al. (1979), for the pulmonary circulation. The true physiological variations in pressure and flow rate as recorded during respiration will serve as boundary conditions to the model. Once the flow field has been computed in this manner, one may calculate the transport of particles of different sizes and densities which are entrained in this known flow. This proposed decomposition of the problem tacitly implies:

a) the basic "clean air" flow will not be substantially altered by the intake of dispersed particles, and

b) a lack of interaction between particles of differing sizes as they deposit onto the walls of the respiratory tract. This allows the deposition distributions to be summed for given particle size distributions.

The alternative to this more simplified approach would be a fully coupled two-phase treatment of the particle-air equations, including particle-particle interactions in a non stationary two-dimensional flow with rotational symmetry. The zones of possible momentary turbulence and flow re-circulation can be evaluated in terms of corresponding losses in stagnation pressure due to viscous dissipation for given bifurcation angles and parent-daughter area ratios. Nondichotomous branching may impose additional difficulties, leading to the necessity of discretizing groups of similar airway generations into equivalent simplified networks.

Such an approach should constitute a substantial improvement over the analysis of Taulbee and Yu (1975), wherein the airway geometry was presumed to be bounded by rigid walls. Laminar flow was considered exclusively, and axial diffusion and particle deposition in the mouth and trachea were neglected. The effects of airway bifurcations on viscous dissipation and total pressure losses were not dealt with in that formulation.

6. ORDER-OF-MAGNITUDE ANALYSIS OF PULMONARY FLOW PARAMETERS: RELATIVE IMPORTANCE OF UNSTEADINESS

Pulmonary airflow and the response of the respiratory system to the uptake of toxicants constitute a highly complex biological system which is extremely difficult to analyze. Within an intricate and truly three-dimensional network of branching distensible conduits, oscillatory flow phenomena occur over a wide spectrum of interacting frequencies. It is therefore not surprising that applied bio-mathematicians seek to capture the primary flow mechanisms within a simpler analogous system which is more tractable to computational solution and which, nonetheless, retains the salient features of the observed physiological response (Jan et al. 1989).

In particular, it is the presence of time derivatives (unsteadiness) in the governing mathematical equations that greatly complicates the solution. If one could, for example, determine flow regions over which the unsteady terms played a lesser role than do other terms in the same transport equations, then the flow could be considered as *quasi-steady,* permitting considerable simplification of the mathematical solution. By quasi-steady, one means that notwithstanding the time-varying flow rates, the detailed characteristics of the flow at any instant (snapshot) in time "adjust" themselves immediately to temporal changes in the external flow conditions. Flow fields then would be identical to those that would obtain in a truly steady flow *at the same flow rate at that instant of time.* In other words, no "inertial" influence or time lag due to the unsteadiness of the flow would be discernible.

Pedley et al. (1986) have shown that for a lung idealized as a branching network of rigid, self-similar bifurcations, the purely oscillatory flow of an incompressible fluid may be characterized by just two

independent dimensionless groups; namely, a dimensionless frequency α^2 and a stroke length parameter L/a, where a is the airway radius, ν the kinematic viscosity and ω the oscillatory frequency. L is the average axial displacement of a fluid particle. Almost all other dimensionless groups found in the literature can be formed from combinations of these two. They have been summarized in Table 1 appearing in the Appendix (Jan et al. 1989). For the human airways, with normal breathing at relatively low frequencies, the dimensionless frequency ranges between $0.01 < \alpha < 3$, with amplitudes between $100 < L/a < 2000$.

Over recent years, a parallel body of relevant literature has developed in response to interest in high-frequency ventilation, characterized by $0.2 < \alpha < 20$ and $20 < L/a < 500$. Indeed, almost 80 years ago, Hendersen et al. (1915) demonstrated that fresh air could reach the other end of the respiratory tract with a smaller flushing volume than the anatomical dead space. This high-frequency regime is of interest because stroke volumes can be reduced by a factor of 4 or 5 while the breathing frequency rises by factors of 7 to 20. Study of this regime was motivated by the need to provide assisted ventilation in the treatment of various respiratory pathologies characterized by reduced tidal volumes and low peak inspiratory airway pressures. It is not unexpected that investigations of high-frequency ventilation have spurred on developments leading to a better understanding of the physiological range of respiratory parameters as well.

Pedley et al. (1986) have reviewed the earlier literature on pulmonary fluid dynamics in which steady and quasi-steady inspiratory flows were studied. Without entering into the full technical details in this succinct report concerning the classical theory of unsteady flows of a viscous compressible fluid, the main physical ideas will be presented for readers not having a specialized background in the field.

As flow develops within a cylindrical tube such as a pulmonary bronchus, the air velocity varies across the tube, from zero at the walls (to which the air particles adhere due to viscosity) to a maximum value at the tube axis. The more slowly moving fluid layer adjacent to the tube walls forms a *boundary layer,* which may be thin relative to the tube diameter, if the *Reynolds number Re* (ratio of inertial to viscous forces) is high, or may fill the tube progressively as in fully-developed *Poiseuille flow* characterized by smaller Reynolds numbers.

Beneath this steady (Blasius) viscous boundary layer may lie a thinner unsteady (Stokes) viscous layer. These boundary layers are of special interest at bifurcations where the flow streamlines curve in passing from a parent to a daughter conduit during inspiration as well as the reverse during expiration. At such bifurcations, most of the pressure losses and gas mixing occur.

It is suggested that a parameter characterizing the intrinsic degree of unsteadiness of a flow may be based on the ratio

$$\epsilon \sim L_g / L$$

where L_g is the length of a generation of conduits and L is the average axial displacement of a fluid particle, and is equal to the stroke volume divided by the local cross-sectional area. Such a parameter ϵ or its variant ϵ^* may be interpreted physically as the ratio of either:

[ϵ^*] (i) unsteady (local) acceleration to the convective acceleration, or

[$\epsilon/4$] (ii) path length of a generation of conduits to the fluid displacement over an oscillatory half-cycle (inspiration/expiration), or

[$\epsilon^{1/2}$] (iii) time required for the thickness of the unsteady Stokes viscous boundary layer to reach the thickness of the steady Blasius viscous layer associated commonly with Poiseuille flow.

The nonlinear differential equations governing fluid motions are given in vector notation in the Appendix and will not be repeated here. They represent: (a) conservation of mass of an incompressible fluid and (b) conservation of momentum. The latter is simply a statement of Newton's law: force = mass $\times$ acceleration. The forces are viscous friction (between adjacent particles and between air particles and the conduit walls) and centrifugal (forces transverse to curved streamlines) in addition to the pressure gradients present in the flow. The acceleration has both *temporal* (measured at a fixed position) and *convective* (measured at a fixed time) components, as indicated in Table 1 of the Appendix.

By comparing like magnitudes of these terms in a classical manner, one is able to establish the existence of at least three flow regimes as depicted in Fig. 1 (Appendix). The details given in the Appendix will be self-explanatory for a reader having an introductory background in fluid mechanics.

Jan et al. (1989) have carried out detailed flow experiments on a plexiglass model of a pulmonary bifurcation, measuring the full 3-dimensional unsteady flow field for a wide variety of flow conditions. The results will be (simplistically) summarized below for the non-specialized reader.

To ascertain whether a flow is quasi-steady, one must consider how quickly that flow will "re-adjust" or become compatible with a sudden time-change in the pressure gradient. In the absence of swirling secondary flows associated with curved tubes (centrifugal forces), the flow can only readjust to a change in the pressure gradient by diffusing vorticity (or equivalently, momentum) through viscous forces over the cross-section of the airway. The time required is approximately a^2/ν. With the addition of the secondary flows described above for curved streamlines, the flow can adjust more quickly because of the associated convective mixing. This

speeds up the process to a time of the order of a/V_s. Here, a is the airway radius, v is the kinematic viscosity and V_s is the cross-flow velocity. Since $a^2/v > a/V_s$, the flow is certainly quasi-steady whenever the larger possible value of the readjustment time

$$a^2/v < 1/\omega$$

or alternatively, when

$$\alpha^2 = \frac{a^2\omega}{v} < 1$$

This implies that flow can be considered to be quasi-steady in parts of the convective flow regime III pictured in Fig. 1 (Appendix). Implications for the quasi-steady uptake of gases in this region III will now be discussed very briefly.

As flow reverses during the transition from inspiration to expiration (and vice versa), significant fluid mixing occurs within the recirculating patterns of vorticity which form momentarily near the walls of the flow divider. Ideally, maximum lateral mixing over the complete tube cross-section will follow immediately upon the reversal in direction of an axial peaked "tongue" of convected fluid. An effective axial diffusivity can be formulated for such a transport process that varies as the square of the tidal volume times the oscillation frequency (Permutt et al. 1985).

6.1 PULMONARY MODELING IN REGIONS I, II and III

It is suggested that flows in the unsteady zone I (Fig. 1) for which stroke lengths are short and secondary motions small, be modeled according to the now classical linearized theory of Womersley (1955). One can assume Poiseuille-type flow everywhere in the viscous zone II where secondary flows are negligible and the *Reynolds number Re* <30 (indicating very little inertia).

The convective zone III may be further subdivided roughly into a very complex turbulent region which has not yet been modeled. In this subregion, unsteady effects, though not dominant, may nonetheless flare up during brief periods of flow acceleration. They are, however, much weaker at peak flow or during decelerative phases. Outside that subregion, inspiratory flow could be modeled as an entrance-length transition over which boundary layers gradually build up. Expiratory flow (daughter-to-parent conduits) remains to be modeled.

6.2 UNSTEADY FLOW REGIME

Unsteady transverse secondary flows contribute significantly to the mixing of chemical toxicants with the respiratory airflow, particularly at the sites of tracheobronchial bifurcations at the end and onset of each inhalation and exhalation. This mixing process is itself critically determined by a delicate interplay of the centrifugal forces (U^2/R) on the fluid or solid particles and the transverse components of the temporal acceleration.

For unsteady effects to dominate this mixing process, one requires (see Eq. 8, 9) that $\alpha^2 \gg 1$. This Womersley number will now be evaluated for typical airflows in the human lung at normal breathing frequencies and for accelerated (high frequency) ventilation.

Using an average value of the kinematic viscosity ν of air equal to 1.5×10^{-5} m^2/sec, one can readily compute the Womersley number α^2

$$\alpha^2 = a^2 \omega / \nu$$

for a range of values of airway radius a. Referring to the human morphometric model (whole lung) of Overton (1990) (his Appendix B, p. 317), one notes a wide range of values of radius a from 1 cm at generation 1 to 1/4 at generation 7, decreasing down to 0.015 at the terminal bronchioles of generation 25. Typical values of α^2_g at generation g are presented in Table 2 below: (normal breathing frequencies: rat = 75/min; human = 12/minute)

TABLE 2. ESTIMATES OF THE WOMERSLEY NUMBER AT VARIOUS GENERATIONS (HUMAN)

Generation g	Airway Radius a (meters)	Breathing Frequencies ω Hz	Womersley Number α^2_g
Trachea			
1	1.0×10^{-2}	10, 1, ½, 0.2	100, 10, 5, 2
5	3.3×10^{-3}	1, 0.2	0.67, 0.134
6	2.87×10^{-3}	1, 0.2	0.55, 0.11
7	2.17×10^{-3}	1, 0.2	0.31, 0.062
25	3.0×10^{-4}	1, 0.2	6×10^{-3}, 1.2×10^{-3}
Terminal Bronchioles			

From these preliminary estimates, it is clear that unsteadiness ($\alpha^2 \gg 1$) in human respiration at normal breathing frequencies is inherently evident in the first few generations distal to the trachea. As breathing frequency increases as a result of work, exercise or neurogenic factors, etc., the importance of unsteadiness

will extend down to the higher generation airway segments as well. This extension is readily estimated by noting that α^2 increases linearly with breathing frequency ω.

In contrast to the human, the Womersley number α^2_g for the rat is shown in Table 3 to be consistently much less than unity at normal breathing frequencies for all generations of the respiratory tract, including the first few generations distal to the trachea.

TABLE 3. Estimates of the Womersley number at various generations (rat)

Generation g	Airway Radius a (meters)	Breathing Frequencies ω Hz	Womersley Number α^2_g
Trachea			
1	1.7×10^{-3}	1	0.193
5	8.1×10^{-4}	1	4.39×10^{-2}
6	6.7×10^{-4}	1	3.00×10^{-2}
7	6.1×10^{-4}	1	2.49×10^{-2}
25	4.3×10^{-5}	1	1.23×10^{-7}
Terminal Bronchioles			

This difference with human response is due to smaller airway diameters for the rat. These diameters appear squared in the expression for the Womersley number and therefore outweigh the approximately 5-fold increase in the rat's normal breathing frequency (1 Hz) relative to the human (0.2 Hz) used in these calculations.

This important finding would indicate that respiratory airflow is essentially quasi-steady throughout the totality of the respiratory tract of the rat, whereas this is not so for the human. Accordingly, respiratory testing of toxicant uptake in the rat may not always display the same qualitative flow regimes observable in the human upper airways (see Fig. 1). Extrapolations of data taken on the rat to assess human response should take these significant differences into account in an appropriate manner.

In the models developed by Ramsey and Andersen (1984) and by Overton (1990), the anatomy of the pulmonary airways has been "lumped" into at least three compartments associated with the upper respiratory tract (URT), the tracheobronchial (TB) region and the pulmonary region, respectively.

Furthermore, good agreement with experimental data was achieved by Ramsey and Andersen (1984) only after fitting the model simultaneously to data from four experiments in order to determine compatible sets of physiological parameters. Even though such estimated model parameters may be reasonable, it is important to verify that they will hold also for widely different experimental data to which they have not been fitted. The

true value of a model lies in its ability to predict response to a wide range of operating conditions well beyond those envisaged in its formulation with experiment.

Generalized models can certainly be improved substantially for more accurate predictions of sudden exposure and/or cessation of exposure to chemical toxicants by incorporating a realistic unsteady analysis into the URT and possibly the TB compartments of the Overton model. In addition, realistic geometry reflecting the anatomical details of the respiratory tract should be incorporated into the models at all levels, if possible.

Finally, basic physiological parameters should be estimated by direct measurement wherever possible, and not obtained through fitting of model results to experimental data. If several parameters are fitted simultaneously in such a process, it is not at all guaranteed that the parameter determination will be unique!

6.3 IMPLICATIONS FOR THE EXTRAPOLATION OF TOXICOLOGICAL ANIMAL TEST RESULTS TO HUMANS

From this very preliminary survey of modeling of pulmonary airflows, it becomes abundantly clear that:

1) current quasi-steady PBPK models for estimation of the uptake of chemical toxicants in small animals, typically rats, must correspond to the particular flow regime(s) prevailing in the animals,

2) the flow regimes applicable to human pulmonary uptake of given toxicants must exist in the animal tests as a necessary, if not sufficient, condition for evaluating quantitatively the same toxicant transport mechanisms of interest to human uptake.

Compliance with these essential requirements may, in some cases, require careful reconsideration of the basic design of particular animal testing programs.

6.4 FUTURE WORK

It would be very worthwhile to formulate a detailed respiratory model of the human lung based upon a branching network of distensible pulmonary airways. Species equations for each of the chemical constituents can then be incorporated and metabolic rate functions assigned locally. Model results may then be compared quantitatively with those of the previous compartmental models as a standard for evaluation of accuracy in assessing risk due to uptake of chemical toxicants via the respiratory tract.

REFERENCES

Chang, H.K. 1986. High frequency ventilation by transthoracic oscillation. In: L.H. Hamilton et al., (eds.) *High Frequency Ventilation* pp. 49-59, Boca Raton: CRC Press.

Chang, H.K., M.E. Weber, and M. King. 1987. Mucus transport by high-frequency non-symmetrical oscillatory air flow. *J. Appl. Physiol.*

Collins, R. and Y. Kivity. 1978. Dynamic rheology of viscoelastic tubes. *J. Biorheol.* 15:173-179.

Collins, R. and J.A. Maccario. 1979. Blood flow in the lung. *J. Biomech.* 12:373-395.

Dreschler, D.M. and J.S. Ultman. 1984. Cardiogenic mixing in the pulmonary conducting airway of man? *Respir. Physiol.* 56:37.

Fredberg, J.J. and A. Hoenig. 1978. Mechanical response of the lungs at high frequency. *J. Biomed. Engrg.* 100:57-66.

Gearheart, J.M., C.S. Seckel, and A. Vinegar. 1993. *In vivo* metabolism of chloroform in B6C3F1 mice determined by the method of gas uptake: The effects of body temperature on tissue partition coefficients and metabolism. *Toxicol. Appl. Pharmacol.* 199:258-266.

Goldberg, I.S. and R.B. Smith. 1981. Settling and diffusion of aerosol particles in small airways during breath holding. *Ann. Biomed. Engrg.* 9:557-575.

Hamilton, L.H. 1986. Historical development of high frequency ventilation. In: L.H. Hamilton, J. Neu, and J.M.Calkins, eds. *High Frequency Ventilation.* pp. 1-12, Boca Raton: CRC Press.

Henderson, Y., F.P. Chillingsworth, and J.L. Whitney. 1915. The respiratory dead space. *Am. J. Physiol.* 38:1.

Hext. P.M. and I.P. Bennett. 1993. Inhalation Toxicology. In: B. Ballantyne et al., eds. *General & Applied Toxicology*, Vol. 1, pp 453-465. New York, NY: Stockton Press.

Jan, D.L., A.H. Shapiro, and R.D. Kamm. 1989. Some features of oscillatory flow in a model bifurcation. *J. Appl. Physiol.* 67(1):147-159.

King, M., D.M. Phillips, A. Zidulka, and H.K. Chang. 1984. Tracheal mucus clearance in high-frequency oscillation. II. Chest wall versus mouth oscillation. *Am. Respir. Dis.* 130:703.

Landahl, H.D. 1950. On the removal of air-borne droplets by the human respiratory tract: I. The lung. B*ull. Math. Biophys.* 12:4356.

Lehr, J. 1980. Circulating currents during high-frequency ventilation. *Fed. Proc.* 39:576.

Leung, H-W. 1993. Physiologically-based pharmacokinetic modeling. In: B. Ballantyne, T. Marrs, and P. Turner, eds. *General & Applied Toxicology*, Vol. 1, pp. 153-164, New York, NY: Stockton Press.

Mitzner, W. 1986. High frequency ventilation: Why it works. In: L.H. Hamilton, et al., eds. *High Frequency Ventilation*, pp. 13-20, Boca Raton: CRC Press.

Morrow, P.E. 1960. Some physical and physiological factors controlling the fate of inhaled substances. I. Deposition. *Health Phys.* 2:366-378.

Overton, J.H. 1990. Respiratory tract dosimetry model for air toxics. *Toxicol. Industr. Health* 6(5):171-180.

Pedley, T.J. and J.M. Drazen. 1986. Aerodynamic Theory. In: *Handbook of Physiology*. The Respiratory System. Mechanics of Breathing. Bethesda, MD., *Am. Physiol. Soc.*, Sect. 3, Vol. III, pt. 1, chapt. 4, pp. 41-54.

Permutt, S., W. Mitzner, and G. Weimann. 1985. Model of gas transport during high-frequency ventilation. *J. Appl. Physiol.* 58:1956-1970.

Ramsey, J.C. and M.E. Andersen. 1984. A physiologically-based description of the inhalation pharmacokinetics of styrene in humans and rats. *Toxicol. Appl. Pharmacol.* 73:159-175.

Schroter, R.C. and M.F. Sudlow. 1969. Flow patterns in models of the human bronchial airways. *Respir. Physiol.* 7:341.

Slutsky, A.S. 1981. Gas mixing by cardiogenic oscillations: A theoretical quantitative analysis. *J. Appl. Physiol.* 51:1287.

Taulbee, D.B. and C.P. Yu. 1975. A theory of aerosol deposition in the human respiratory tract. *J. Appl. Physiol.* 38:77-85.

Vinegar, A., K.L. Auten, C.S. Seckel, Y.M. Reed, and R.B. Conolly. 1990b. Physiologically-based pharmacokinetic model of the metabolism of trichloroethylene by an isolated ventilated perfused lung. *Inhal. Toxicol.* 2:285-294.

Vinegar, A., D.W. Winsett, M.E. Andersen, and R.B. Conolly. 1990a. Use of a physiologically-based pharmacokinetic model and computer simulation for retrospective assessment of exposure to volatile toxicants. *Inhal. Toxicol.* 2:119-128.

West, J.B. and P. Hugh-Jones. 1961. Pulsatile gas flow in bronchi caused by the heart beat. *J. Appl. Physiol.* 16:697.

Womersley, J.R. 1955. Method for the calculation of velocity, rate of flow and viscous drag in arteries when the pressure gradient is known. *J. Physiol. Lond.* 127:553-563.

Yu, C.P. and C. Thiagarajan. 1979. Decay of areosols in the lung during breath holding. *J. Aerosol Sci.* 10:11-19.

APPENDIX

NONSTATIONARY FLOW IN THE LUNG

Order-of-Magnitude Analysis of Dominant Flow Regimes

NONSTATIONARY FLOW IN THE LUNG

In order to interpret the qualitative features of different flow regimes which may develop within the respiratory tract, it is very helpful to formulate an overall classification scheme based upon an order-of-magnitude analysis of the underlying fluid dynamic equations. These equations, representing conservation of mass and momentum, are constituted by a system of nonlinear partial differential equations with initial and boundary conditions. For the purposes of this preliminary analysis, these will be expressed below for axially symmetric flow:

$$div\ \vec{V} = 0$$

$$\frac{\partial \vec{V}}{\partial t} + V grad \vec{V} = -\frac{1}{\rho} grad\ p + \nu\ div\ grad \vec{V}$$

where V is the velocity vector and p the pressure in the airflow. The second vector equation represents a simple force balance between temporal acceleration, convective acceleration, pressure gradient and viscous forces, respectively. For axially symmetric flows, they reduce, without loss of order-of-magnitude generality, to

$$\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} = 0$$

$$\frac{\partial u}{\partial t} + u\frac{\partial u}{\partial x} + v\frac{\partial u}{\partial y} = -\frac{1}{\rho}\frac{\partial p}{\partial x} + \nu\frac{\partial^2 u}{\partial y^2}$$

$$\frac{\partial v}{\partial t} + u\frac{\partial v}{\partial x} + v\frac{\partial v}{\partial y} = -\frac{1}{\rho}\frac{\partial p}{\partial y} + \nu\frac{\partial^2 v}{\partial y^2}$$

where $V(\mu,\nu)$ denotes the axial and transverse components of the fluid velocity respectively, in the x and y directions. These various terms can be usefully displayed (Jan et al. 1989) in tabular form as

TABLE 1. ORDER-OF-MAGNITUDE ESTIMATES OF AXIAL AND SECONDARY FLOW COMPONENTS

	Axial Flow Equation		
	Temporal (unsteady)	**Convective**	**Viscous**
Representative terms	$\frac{\partial u}{\partial t}$	$u\frac{\partial u}{\partial x}, \quad v\frac{\partial u}{\partial y}$	$\nu\frac{\partial^2 u}{\partial y^2}$
Order-of-magnitude estimates	ωU	$\frac{U^2}{Lg}, \quad \frac{V_s U}{a}$	$\frac{\nu U}{a^2}$

	Secondary - Flow Equation			
	Temporal	**Convective**	**Centrifugal**	**Viscous**
Representative terms	$\frac{\partial v}{\partial t}$	$u\frac{\partial v}{\partial x}, \quad v\frac{\partial v}{\partial y}$	$\frac{u^2}{R}$	$\nu\frac{\partial^2 v}{\partial y^2}$
Order-of-magnitude estimates	ωV_s	$\frac{V_s U}{Lg}, \quad \frac{V_s^2}{a}$	$\frac{U^2}{R}$	$\frac{\nu V_s}{a^2}$

The transverse secondary flows are primarily of a swirling nature. In the pulmonary airways, it is they that are largely responsible for the mixing of chemical toxicants with air. Such flows are particularly sensitive to bifurcation angles and radius of curvature, as they engender centrifugal forces on fluid and solid particles entrained in such flows. Under certain circumstances to be identified, these swirling flows may be characterized by an inherent unsteadiness. In this case, the centrifugal forces caused by particles following a curved trajectory are offset by temporal accelerations, such that

$$V_S \omega \sim U^2/R$$

where V_S is the secondary velocity scale, U an axial velocity scale, and R a radius of curvature of the particle trajectory within the airway. Adopting a generation length L, an airway radius a and a breathing frequency ω, one obtains an order-of-magnitude estimate of the secondary velocity

$$V_S/U \sim U/\omega R = L/a \times a/R$$

where

$$U = L\,\omega/2.$$

From the observation that the transverse accelerations $V_s\omega$ are much larger than either the convective accelerations or the viscous forces, it follows that, for a typical human airway bifurcation with a/L = 1/7, and a/R = 0.1, the Womersley number $\alpha^2 = a^2\omega/\nu$ must be much larger than one, if the flow is to be dominated by unsteadiness.

Similar order-of-magnitude analyses have been carried out by Jan et al. 1989 for the viscous and convective-dominated flow regimes.

Their results are aptly summarized in Figure 1 below:

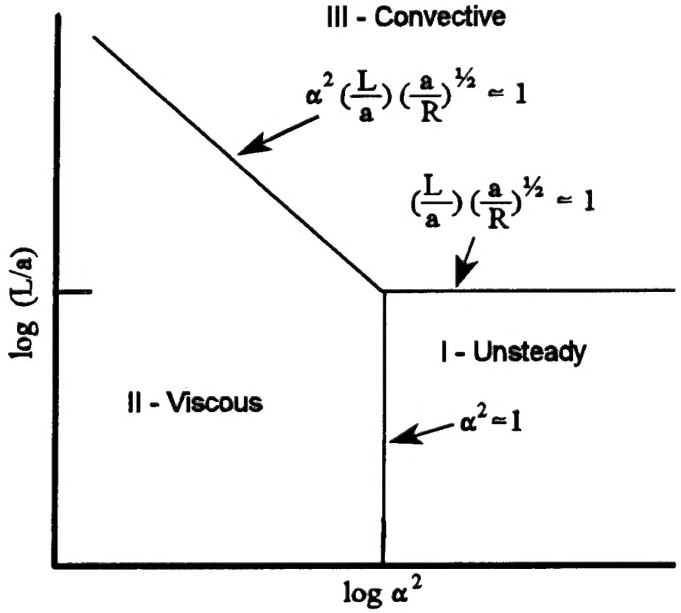

Figure 1. Flow regimes based on order-of-magnitude analysis mapped onto a log scale. The 3 limiting regimes are I (unsteady), II (viscous), and III (convective), defined in terms of effects that dominate in each zone. See text for further explanation.

By locating the flow regime applicable to given animal or human tests within the context of the above Figure 1, it is straightforward to classify those flows within the aforementioned boundaries as being dominated either by viscous, convective accelerative or unsteady forces. Extrapolation of such test results should only be logically carried out amongst species in which the same flow regime applies.

U. S. Government Printing Office 1995 650-075/00094